Focal Ablation of Prostate Cancer

NYU Case of the Month, June 2018

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[Rev Urol. *2018;20(2):107–111 doi: 10.3909/riu0812*]

A 61-year-old man presented with an elevated and rising prostate-specific antigen (PSA) level. The rising PSA level was confirmed:

- 10/2012: 6.4 ng/mL
- 3/2016: 11.1 ng/mL
- 3/2016: 10.7 ng/mL

Evaluation

Digital rectal examination (DRE) revealed a left mid/base 1-cm nodule with no extracapsular extension (clinical stage T2A). Sexual Health Inventory for Men (SHIM) score was 25 and International Prostate Symptom Score (IPSS) was 1.

Because of the elevated and rising PSA and the prostate nodule, an MRI was obtained. The MRI demonstrated a 10 × 8 mm PI-RADS 3 lesion of the medial aspect of the left anterior base/ mid transition zone. A low signal intensity lesion is seen in the left transition zone on the T2-weighted (Figure 1a) and diffusion-weighted (Figure 1b) images. The dynamic contrast enhancement image (Figure 1c) shows rapid uptake of the lesion. Together, these findings are consistent with a PI-RADS 3 lesion. The prostate volume was 44 cm^3.

Magnetic resonance fusion-target biopsy (MRFTB) and 12-core computer-generated systematic biopsy (SB) were performed using the Artemis platform. Antibiotic prophylaxis included ciprofloxacin for 3 days and ceftriaxone 1 g intramuscularly at the time of biopsy.

- **MRFTB 4 cores:** 2 cores positive for Gleason Grade Group (GGG) 1 (greatest core length 8 mm)
- **SB:** Left medial apex 1 mm GGG2; right medial base 0.5 mm GGG1.

Based on the biopsies alone, the patient would be a candidate for active surveillance

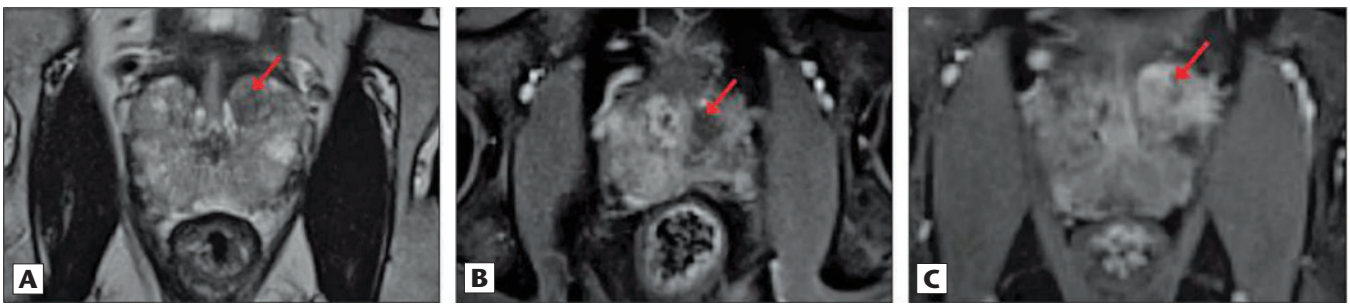

Figure 1. Presurgical MRI showing a PI-RADS 3 lesion.

(AS). However, the rising PSA, the prostate nodule, and the PI-RADS 3 lesion suggested the disease was clinically significant for a 61-year-old man and likely under-graded. The high PSA is characteristic of transition zone cancers.

Management

The patient was reluctant to undergo radical prostatectomy (RP) or radiotherapy (RT) because of the potential adverse impact on sexual function, and because he was a candidate for focal ablation (FA), he elected this option.

Because of the anterior location of the disease, focal cryoablation was the preferred energy source. Cryoablation was performed with three freezing probes, which allowed for ablation of the MRI lesion with a 10-mm margin. Temperature probes were placed along the left neurovascular bundle to ensure temperatures at this location would not go below 0°C. A temperature probe was placed at the left anterior margin of the prostate as a margin and registered –40°C. Anesthesia time was 2.5 hours, a Foley catheter was left indwelling, and the patient left the hospital 3 hours after arriving in the recovery room.

The catheter was removed on post-procedure day 4, with no subsequent urinary retention. He returned to work 5 days after the procedure.

Six months following focal cryoablation, the patient's PSA was 2.6 ng/mL and his IPSS and SHIM were 1 and 25, respectively. A 6-month MRI showed a non-enhancing ablation cavity (Figure 2a), which was interpreted to be non-suspicious for in-field disease, and a PI-RADS 2 lesion in the right transition zone not previously seen (Figure 2b).

Because of the pre-ablation GGG1 0.5-mm tumor and the new PI-RADS 2 lesion, four biopsies each were targeted into and around the ablation cavity and the new PI-RADS lesion. SBs were also performed, using the Artemis computer template. No cancer was seen in any biopsy specimen and the ablation cavity and several SB specimens from the left biopsies showed tissue ablation effects.

Discussion

Is There a Role for Focal Ablation of Prostate Cancer?

Given prostate cancer's unique characteristics, namely, the spectrum of the disease aggressiveness, the life expectancy range of those affected, and the balance of treatment priorities between oncological control and functional outcomes, it is reasonable for the optimal management of prostate cancer to include AS, whole-gland treatments (RP and RT), and an alternative that offers a relative balance between oncological control and preservation of quality of life, and that alternative would be FA.

FA of prostate cancer includes any ablative treatment that partially destroys the prostate gland. The extent of ablation can be the MRI lesion only, the MRI lesion plus a margin, hemi-ablation, or subtotal ablation. The optimal extent of ablation has yet to be established. Increasing the extent of ablation will have some adverse effects on sexual outcomes with reciprocal benefit on oncological outcomes.

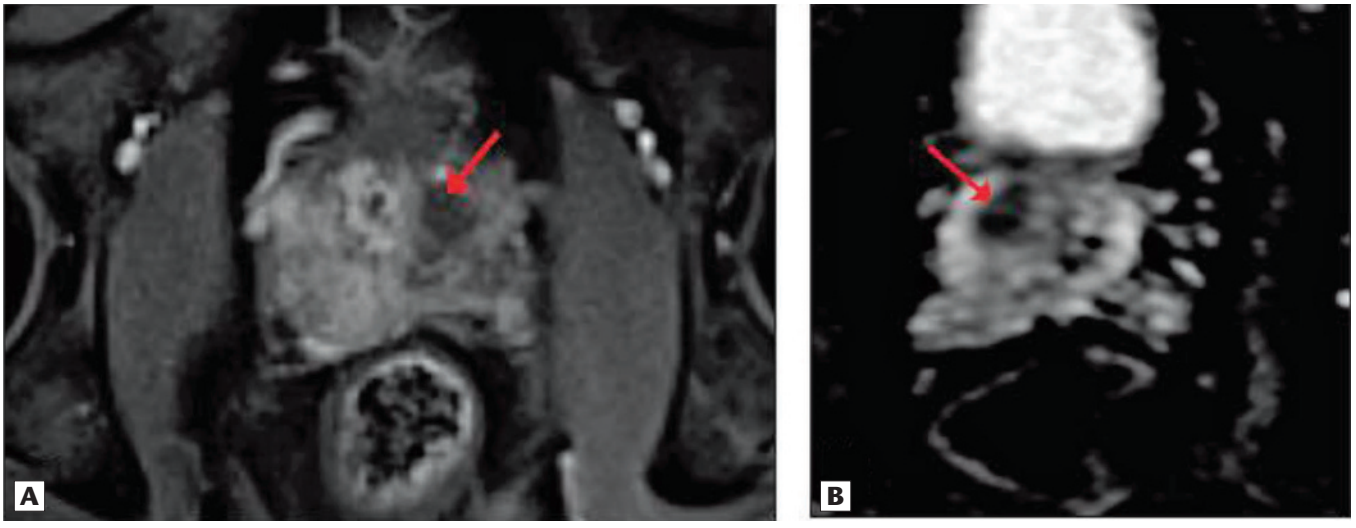

Figure 2. Postsurgical MRI.

Issues in Focal Ablation of Prostate Cancer: Untreated GGG1 Disease Following Focal Ablation

The selection of candidates for FA based on MRI will leave untreated GGG1 disease. Adoption of focal therapy (FT) assumes untreated low-risk disease poses no immediate adverse oncological risk. This concept is the justification of AS for GGG1 disease.

MRI Identification of the Index Lesion

Most prostate cancers managed by RP are multifocal. Fortunately, the aggressiveness of prostate cancer is typically defined by a single index tumor representing the cancer with the highest GGG and pathological stage. MRI reliably identifies the index cancer in more than 85% of men undergoing RP.

Rarity of MRI/MR Fusion Target Biopsy/Systematic Biopsy Missing Significant Disease

The selection of candidates for FA should include a high-quality multiparametric MRI, MRFTB of the MRI lesion confirming cancer, and contralateral SB showing no >GGG1 disease. At NYU Langone Health,[1] we identified 59 men who fulfilled these selection criteria for FA who underwent RP at our institution. MRI, MRFTB, and SB were performed on all candidates prior to RP. The surgical specimens were step-sectioned, and all cancers were identified and mapped. The presence of any Gleason pattern 4 disease outside two hypothetical ablation zones was identified. If these men had undergone FA with a planned ablation template of MR lesion +10-mm margin or hemi-ablation, the likelihood of leaving any Gleason pattern 4 disease would have been 19% and 23%, respectively. The Gleason pattern 4 disease was consistently less than 1 mm in length.

Ability to Deliver Ablative Energy to Predefined Targets

Most in-field biopsies following FA show no significant cancer within a year after treatment, suggesting that ablative energy is being effectively delivered to the designated target. Whether untreated disease within or beyond the ablation zone will become problematic over time requires further investigation and represents an important FA consideration.

Quality of Life: An Important End Point

A large prospective Swedish study[2] reported rates of incontinence following RP (defined as use of 2 or more pads a day) of 20% and 21% after open and robotic RP, respectively. The likelihood of an International Index Erectile Function (IIEF) score <17 was 81% and 77% following open and robotic RP, respectively. Barry and colleagues[3] reported similar results in a survey of RPs performed in the US Medicare population. In our large series of more than 300 FAs at NYU Langone, we have rarely observed urinary incontinence and erectile dysfunction at 6 months following FA consideration.

Selecting Candidates for Focal Therapy

All candidates for FT should undergo MRI, MRFTB, with SB or transperineal saturation biopsy (TPSB) to map the disease. I offer FT to men with a single MRI lesion without gross extracapsular extension who have high-volume GGG1, any volume GGG2-GGG3, and, in very select cases, GGG4 disease. In most cases, I will exclude cases with low-volume contralateral GGG2 disease. I believe there is a reasonable probability that men with long life expectancies will develop significant in-field disease in the untreated prostate over time. In these cases, AS, repeat FT, RP, and RT are all potential salvage treatments. For many men, deferring whole-gland treatment is a desirable option providing the development of metastasis or death is not an adverse consequence of delayed intervention.[4]

Ablative Energy Sources

There are many ablative energy sources for FT of prostate cancer. The treatment most extensively used in the United States for FT is cryoablation. The two cryoablation systems on the market (from HealthTronics, Inc, Austin, TX and Galil Medical, Arden Hills, MN) both use freezing probes placed under ultrasound guidance. We have recently used a system that allows the performance of cryoablation using MRI/ultrasound fusion technology. Temperatures within the ablation zone reach as low as –70°C. Cell death reliably occurs at –40°C and is often achieved at –20°C. The extent of tissue destruction is controlled by observing in real time the leading ice, which is 0°C. Temperature probes placed strategically ensure that temperatures of –20°C are achieved at the intended margins while protecting the rectum, external sphincter, and, in selected cases, the neurovascular bundles from damage. An advantage of cryoablation over high-intensity focused ultrasound (HIFU) is that site of disease, prostatic calcifications, and, to a lesser degree, prostate volume are not limitations to its

clinical application. We have performed cryoablation on a 250-g gland in a 58-year-old man with a BMI of 46.

HIFU uses a transrectal ultrasound probe to deliver thermal energy to the prostate, resulting in coagulative necrosis. The two HIFU delivery systems available in the United States are the Sonablate 500 (SonaCare Medical, Charlotte, NC) and the EDAP Focal One (EDAP TMS, France). Limitations of both HIFU systems are larger prostate size, prostatic calcifications, and anterior lesions. At NYU Langone, we prefer the Sonablate system because it offers far more versatility for controlling every energy pulse. The wattage can be modified based on observed near-field changes and whether the tissue control monitoring indicates failure of energy delivery to the target. HIFU is ideal for posterolateral lesions in smaller glands in men for whom preservation of potency is a high priority. HIFU allows more precise delivery of energy and, theoretically, better confluence of the ablation zone than intra-prostatic probes.

The mechanism for cell kill in irreversible electroporation (IRE) involves creating an electrical current between two probes positioned under ultrasound guidance. The cell kill is independent of temperature. A theoretical advantage of IRE is that prostate tissue adjacent to the urethra can be destroyed while avoiding injury to the urethra, thereby avoiding tissue sloughing.

Vascular targeted photodynamic (VTP) therapy has been studied in Europe and South America. A photosensitizer (TOOKAD Soluble VTP, Steba Biotech S.A.) is injected intravenously and prostate tissue is destroyed by activating the photosensitizer via transperineally placed laser probes. Activation of the photosensitizer leads to formation of free radicals and then to microvascular thrombosis. The limitations of VTP are the injection of a photosensitizer and the ability of laser probes to achieve confluence of cell death.

Radiofrequency is a novel technology that very precisely delivers ablative energy to the prostate. A corkscrew cage is manipulated into the prostate under ultrasound guidance. A unique feature of radiofrequency energy is the very precise demarcation between the ablated and the normal tissue. The challenge is optimal placement of the radiofrequency cage and contouring cage placement to the configuration of an intended ablation template.

We have investigated laser energy without activating a photosensitizer to ablate prostate cancer. These diode lasers produce thermally induced coagulative necrosis. The laser fibers are placed transrectally under MRI guidance under local anesthesia with oral sedation. The primary limitation of laser ablation is creating a confluent lesion because only one laser fiber is used at a time due to the cost of the individual fibers. Another limitation is patient comfort because the patient may be lying prone in the MRI machine for more than 2 hours.

Outcomes of Focal Ablation

All the energy sources used for FT of prostate cancer are designed to be used in outpatient procedures performed either under sedation with a prostate block or under general anesthesia. The use of general anesthesia is at the discretion of the surgeon rather than determined by inherent properties of the energy source. At NYU Langone, we have performed cryoablation, HIFU, radiofrequency, and VTP under general anesthesia because we have this capability in our office-based operating room. Independent of energy source, about 3 hours after the procedure, patients are discharged from the outpatient facility with an indwelling Foley catheter. Depending on the volume of tissue ablation, baseline prostate volume, and underlying lower urinary tract symptoms, a voiding trial is scheduled 3 to 5 days after the procedure. Unsuccessful trials of voiding are atypical. Men usually return to employment after catheter removal. In more than 300 FA cases performed at NYU Langone, only one patient developed significant incontinence. Use of protective pads even immediately after catheter removal is rare. Because preserving sexual function is a high priority for most men, they need to be counseled that seminal volume may diminish. Although we have observed transient erectile dysfunction in some cases, baseline potency is almost always restored within 6 months. Some men will benefit from phosphodiesterase type 5 inhibitor to restore erections to baseline levels immediately following treatment.

The literature provides an abundance of biopsy-based oncological outcomes within the first year of FA. In-field disease occurs in about 20% of cases and depends on baseline GGG and the number of targeted biopsies performed. There

is a paucity of studies reporting intermediate- and long-term oncological control following FA. Additional major limitations of the FA literature are lack of standardization of both selection criteria and assessment of oncological control. The ability to detect untreated prostate cancer will undoubtedly depend on the number and frequency of biopsies. What is desperately needed is literature on rigorous oncological outcomes, which will ultimately define the role of FA for men with prostate cancer. We previously reported 96% of in-field negative biopsies 6 months after focal laser ablation in 32 cases.[5] At 2 years, all of these men underwent PSA and MRI testing.[6] Overall, 10 men with a non-suspicious MRI refused in-field prostate biopsy. Of the 22 men undergoing in-field prostate biopsy at 2 years, 17 (77%) and 9 (41%) exhibited any cancer or >GGG1 cancer, respectively. Our very preliminary conclusion is that in selected cases the favorable negative predictive value of a negative MRI and a stable PSA for significant prostate cancer may allow for avoiding an in-field biopsy. However, a negative MRI and a stable PSA do not exclude GGG1 disease.

Conclusions

Today, prostate MRI coupled with MRFTB can with reasonable reliability identify the site(s) of clinically significant prostate cancer, and we can direct ablative energy to these predefined sites of disease. Preliminary studies suggest that in selected cases of intermediate-risk disease, good early oncological outcomes are achievable with available ablative energy sources. The important unknown is whether these favorable oncological outcomes will be durable. It is also clear that FA is truly a minimally invasive strategy for localized prostate cancer because it is an outpatient procedure with expedited recovery and virtually no adverse impact on continence. Some men experience a transient decline in erectile function, but potency is restored by 6 months with only diminished seminal volume. For many men, the uncertainty of oncological control and the requirement of a lifetime of surveillance are a small price to pay for preservation of quality of life.

Urologists who embrace FA must collaborate with radiologists well versed in prostate MRI and they must start the learning curve with lower-volume disease. The major potential harm of this minimally invasive procedure is inadequate treatment. Meticulous technique is essential, and patients must agree to surveillance imaging and biopsy. If as a urology community we embrace FA responsibly, we have the potential to advance the field and to benefit our patients. If done irresponsibly, patients will be harmed. ■

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